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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/18/2002

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/627,787	Uhlmann
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 12, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above, claim(s) *3, 6, and 7* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4, 5, and 8-26* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants amendment received 8/12/02 was entered as Paper No. 16.

The previous Office Action is hereby withdrawn in favor of the following non-final action.

Applicant's election with traverse in Paper No. 14 of the species of F3 as an aryl group; oligonucleotides as a compound to be transported; and a carboxylic acid as a reactive function, is acknowledged. Traversal is on the grounds that searching all the disclosed species would not be an undue burden. This is unpersuasive because the required searches would be non-coextensive and because the claimed conjugates are chemically distinct compounds having different structures and functions. The requirement is still deemed proper and is therefore made FINAL

Claims 1-26 remain pending in the Application. Claims 3, 6, and 7 are withdrawn from consideration as being drawn to non-elected material. Although claims 6 and 7 are not under consideration, Applicant's amendment to these claims has been entered as requested.

Applicant is advised that upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a). It is noted that be

Compounds comprising the aryl group denoted as F3, and an oligonucleotide molecule to be transported with a reactive carboxylic acid group, were found to be novel and nonobvious

over the prior art. In accordance with MPEP803.02, the Office has extended the search to a second species of the claimed invention. Claims reciting this species have been found to be anticipated and obvious over the prior art for the reasons given below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is drawn to pharmaceutical compositions and methods of making them. The claimed composition is a conjugate of an aryl compound to an oligonucleotide. MPEP 2164.01(c) states:

> When a compound or composition is limited by a particular use, enablement of that claim should be evaluated based on that use.

In this case, enablement of the claimed composition and method must be evaluated in terms of the use of the composition as a pharmaceutical. The specification fails to define the term "pharmaceutical", so in order to understand how this term limits the invention, one must

determine its accepted meaning in the art. According to Steadman's Medical Dictionary (26th Edition, 1995) "pharmaceutical" means "relating to pharmacy or to pharmaceutics". In the same dictionary, "pharmacy" is defined as a "practice that emphasizes the therapeutic use of drugs rather than the preparation and dispensing of drugs." Finally, Steadman's Medical Dictionary defines "drug" as a "therapeutic agent; any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease in man and animal." Thus, to enable a pharmaceutical use for the claimed composition, the specification must teach how to use the substance, without undue experimentation, for the prevention, diagnosis, alleviation, treatment, or cure a disease in the animal to which the substance is administered.

The specification teaches that the claimed compositions can be used for therapeutic and diagnostic purposes *in vivo*. Therapeutic uses of the claimed composition are discussed at page 24, line 29 to page 25, line 2 and page 25, line 27 tp page 26, line 4. The compositions are asserted to be useful for the prevention and treatment of diseases caused by overexpression of certain genes, particularly viral diseases, cancer, restenosis, and depigmentation diseases. See page 25, line 30 to page 26, line 4. Treatment can be effected by delivery of antisense oligonucleotides; triplex-forming oligonucleotides; "decoy" oligonucleotides which mimic the binding site of transcription factors, titrating these factors and inhibiting binding to their natural targets; and chimeraplasts for site-directed gene modification. Thus the claims broadly embrace the treatment or prevention of any disease caused by gene overexpression.

The state of the art with respect to antisense therapies indicates a high level of unpredictability. Crook (In Basic Principles of Antisense Therapeutics, Springer-Verlag, Eds, New York, pgs. 1 and 4), teaches that although antisense techniques have progressed rapidly, "the technology remains in its infancy", and the utility of the approach is still debatable (pg. 1, Introduction). Crook points out several factors which may influence the biological effect of an antisense oligonucleotide (AODN), including the rate of uptake of the AODN, rate of distribution within the target cell, stability within the target cell, local concentration of the oligonucleotide, and the concentration and stability of the target mRNA (pgs. 1 and 4). Furthermore, Branch (Trends in Biochem Sci 23: 45-50, 1998) teaches that selection of appropriate antisense sequences is difficult because secondary structures of mRNAs *in vivo* frequently restrict access of antisense oligonucleotides to the target sequence (page 45, col. 3. first para., page 48, last para. and page 49). Branch states, "Since accessibility cannot be predicted, rational design of antisense molecules is not possible" (page 49, col. 2, last para.). Ho and Parkinson (Sem. Drug Discov. 24(2): 187-202, 1997) teach that although antisense therapy is simple in theory, it " has proven to be much more complex in practice. A number of important challenges in the preclinical development of antisense oligonucleotides have been identified, including stability, sequence length, cellular uptake, target sequence selection, appropriate negative controls, oligonucleotide: protein interactions, and cost of manufacture." The authors conclude that [c]ontinued progress in this arena will require that many of the preclinical challenges confronting antisense development are satisfactorily resolved." See abstract. Akhtar (J. Antimicrob. Chemother. 38(2): 159-165,

1996) teaches that "a healthy degree of concern exists among scientists and administrators as to whether antisense and, to some extent, ribozyme oligonucleotides will ever become useful therapeutic agents." See page 163, column 1, lines 5-14 of first full paragraph. Thus, at the time the invention was made, there was considerable unpredictability in the design of antisense oligonucleotides, their delivery and pharmacodynamics, and most importantly, whether or not they would ultimately have any therapeutic value.

Gryzanov (Biochim. Biophys. Acta 1489:131-140, 1999) set forth the state of the art with respect to therapeutic applications of triple helix technology. Gryzanov notes that "several important issues remain to be resolved before oligonucleotides may become widely used unique and specific pharmaceutical agents. Among these are: increased thermodynamic stability of the complexes formed by the oligomers with their nucleic acid targets, specificity of the interactions, resistance to enzymatic degradation and hydrolytic stability in cells, in model animal systems, and importantly, favorable pharmacokinetics and biodistribution in human tissues and organs. Additionally, chemical structures of the therapeutic oligonucleotides, cost of synthesis, and the proper choice of suitable and biologically important molecular targets, as well as delivery methods for administration of compounds, will play a crucial role in ensuring success of oligonucleotide-based therapeutic approaches." See page 132, lines 31-37 of column 1 to line 10 of column 2.

The instant invention addresses the aspect of oligonucleotide (ODN) delivery. The specification indicates that the invention serves to (a) improve delivery by increasing the rate at

which ODNs are taken up by cells, (b) circumvent the endocytotic pathway thereby allowing distribution of ODNs to both the cytosol and nucleus, and (c) decrease the damage to cells compared to liposomal delivery compositions. See page 4, line 28 to page 5, line 19. A variety of oligonucleotides designed for the treatment of various diseases is disclosed at pages 13-17. The specification teaches working examples demonstrating the uptake of the claimed compositions into cultured cells *in vitro*. See Tables 1 and 2 on pages 37 and 38, and also Fig. 9.

The specification does not disclose the effect of the compositions on any cell, or provide any working example of any therapeutic effect. No specific therapeutic or preventative protocol for any disease is taught. No specific guidance is given with respect to dosages or routes of delivery for any particular disease. No evidence is provided that the increased rate of uptake, and improved cellular distribution observed in the instant invention are sufficient to overcome the art-recognized problems associated with therapeutic oligonucleotide delivery as set forth by Crook. The specification fails to account for various critical factors which will influence the success of therapy including the varying concentrations and stabilities of the target mRNAs or polypeptides, the thermodynamic stability of complexes formed by the compositions, the specificity of the interactions, stability of the preparations in animal systems, and pharmacokinetics and biodistribution in human tissues and organs. Perhaps most importantly, none of these issues has been considered within the context of any one therapeutic protocol. Because the physiological art is recognized as being unpredictable (MPEP 2164.03), one of skill in the art recognizes that these variables will change with the identity of the disease to be treated

or prevented. However, the specification fails to address the variables cited above in the context of treating or preventing any specific disease. Furthermore, given the unpredictability of oligonucleotide design, as set forth by Branch, it is unclear that any of the oligos taught in the specification will have any therapeutic effect *in vivo*.

Given the unpredictable state of the art of oligonucleotide-mediated therapies, the lack of guidance and working examples in the specification, and the breadth of diseases disclosed as treatable with the claimed compositions, one of skill in the art could not use the claimed invention as intended without undue experimentation.

The specification also teaches that the claimed compositions can be used for *in vivo* diagnosis of diseases caused by the overexpression of genes. See page 24, line 29 to page 25, line 2. However, no guidance is given as to how the claimed compositions may used *in vivo* as a diagnostic. A search of the prior art revealed only two publications related to the *in vivo* use of oligonucleotides for diagnosis, both from the same laboratory. Rusckowski et al (Cancer 80(12)(Supplement): 2699-2705, 1997) and Mardirossian (J Nucl. Med 38(6): 907-913, 1997) teach the use of oligonucleotides in pretargeting techniques. Briefly, a target entity such as a bacterium or a tumor cell was injected in to the left thigh of a mouse, Then an oligonucleotide, conjugated to a molecule with an affinity for the target entity, was injected into the mouse. Subsequently a complementary, radioactively-labeled oligonucleotide was injected and allowed to hybridize to the first oligonucleotide. Although the resulting signal was detected in the target tissue, it was also associated with liver, heart, kidneys, lung, stomach, spleen, intestines and

blood, in amounts greater than in the target tissue. See Rusckowski, Table 1 on page 2702, and Figs. 2 and 3 on pages 2703 and 2704. Clearly the level of false positive signal in these tissues shows that the technique did not have diagnostic value at the time of publication. The instant specification fails to contemplate this specific use for the claimed invention, and thus does not provide any teachings which would improve the technique to the point that it could function as an *in vivo* diagnostic.

Because the specification provides no guidance as to how to use the claimed invention in vivo as a diagnostic tool, and because the state of the art shows that oligonucleotide compositions were not routinely used for this purpose by those of skill in the art, one of skill in the art would have to perform undue experimentation to use the claimed compositions *in vivo* as diagnostics.

This rejection can be overcome by deleting the word "pharmaceutical" from the claims.

Response to Arguments

Applicant's arguments filed 8/12/02 have been fully considered but they are not persuasive.

Applicant asserts at page 3, second paragraph of the response, that the level of predictability of the antisense technology in general is irrelevant to determining enablement of the claimed methods of making pharmaceutical compositions. This is unpersuasive because it is not supported by evidence or reasoning. On the other hand, the first three paragraphs of the rejection explain in detail why use of the word "pharmaceutical" raises the issue of the

predictability of antisense therapeutic methods. Applicant has not shown why this explanation is insufficient.

At paragraph 3 of page 3, Applicant considers the working examples in the specification, but fails to point to any evidence that supports any therapeutic effect of any oligonucleotide.

At page 4 of the response Applicant asserts that pharmaceutically active oligonucleotides are known in the art, relying for support on Dove (2002). As Applicant notes Dove is published after the filing date of the instant application. Applicant is reminded that developments occurring after the filing date of an application are of no significance regarding what one skilled in the art believed as of that filing date. See for example, *in re Wright*, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993). Applicant's assertion that it is reasonable to conclude that compounds in phase II and III clinical trials are pharmaceutically effective is unsupported. See for example Dove at page 122, column 2, first full paragraph, which provides evidence of an antisense compound which progressed to phase III clinical trials and was ultimately found to have no therapeutic effect. Applicant notes that a pharmaceutically effective antisense oligonucleotide, Vitravene, was approved by FDA in 1998. However, this single example of a pharmaceutically effective antisense molecule cannot provide enabling support the instant claims which broadly embrace the treatment or prevention of **any** disease caused by gene overexpression. Furthermore, Dove only underscores the unpredictability of the antisense art at the time of filing, indicating that confidence in antisense therapy approaches tumbled in the late 1990s, and "hit rock bottom late in 1999." See page 122, column 2, lines 5-11. Dove also reinforces the teachings of Branch

regarding the unpredictability of antisense design by stating that "[r]esearchers have found that one key to getting specific inhibition is to target the correct portion of the target RNA sequence, something that appears to be determined by trial and error only." See page 123, column 1, lines 7-11. One might argue that it would not be undue experimentation to assay antisense molecules individually, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to **known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. It is clear that, at the time of filing, there were no known scientific laws that enabled the accurate prediction of which antisense molecules would have pharmaceutical effect.

Applicant points out at page 4 that Table 1 of Crooke and Lebleu shows that a large number of genes have been targeted by antisense oligonucleotides. This is unpersuasive of pharmaceutical efficacy because each of these studies was performed in vitro. As noted more fully below, antisense results obtained in vitro are not necessarily predictive of results in vivo.

The unpredictability of the art of antisense therapy at the time of filing is evident from the art cited above, and it is also clear that this situation persisted after the time of filing as well, due to obstacles that continue to hinder the therapeutic application of antisense in vivo (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February

2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonantisense effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery.... Presently, some success has been achieved in tissue culture, but efficient delivery for in vivo animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods in vivo, with a resultant therapeutic outcome. The specification provides cell culture examples, but these are generally not predictive of in vivo inhibition due to

differences in metabolites and clearance rates, local concentration of antisense, differences in target site accessibility, cellular uptake differences and the potential for non-antisense side effects. Often formulations and techniques for delivery in vitro (cell culture) are not applicable in vivo (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see pages 79-80, section entitled Cellular uptake facilitators for in vitro studies) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides. In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell in vitro versus in vivo, the uptake and biological activity observed in vitro would not predictably translate to in vivo results.

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type in vivo (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to sphingosine-l-phosphate lyase to generally any target cell or tissue in vivo (whole organism) at a concentration effective to provide a pharmaceutical effect or to treat the broad range of diseases encompassed by the claims.

In order to practice the invention claimed over the full scope claimed, i.e. the production of a *pharmaceutical* composition, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of what specific diseases and conditions can be treated by the administration of any antisense oligonucleotide, what specific cells to target with antisense for the treatment of a particular disease or condition, and how to specifically deliver antisense to a target cell in vivo (whole organism) at a concentration effective to result in inhibition of the expression of a target gene to a level sufficient to result in a pharmaceutical effect or to treat a disease. Additionally, this undue experimentation would include the determination of such factors as dosage, route of administration, disposition of the antisense molecule in tissues, and the half life and stability of the antisense molecule in vivo. Given the art recognized unpredictability of the therapeutic application of antisense in vivo (whole organism), this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope embraced by the claims, the state of the art of antisense and triplex technologies, the level of unpredictability of in vivo (whole organism) methods of treatment using antisense, the lack of specific guidance for the in vivo (whole organism) application of antisense methods of treatment and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the invention over the full scope claimed without undue trial and error experimentation.

Applicant's arguments at page 5, first paragraph regarding the usefulness of the invention in conjugating pharmaceutical compounds other than oligonucleotides are irrelevant because the elected invention under consideration requires pharmaceutical oligonucleotides.

Applicant argues at page 5, third paragraph that it is not necessary to provide guidance with regard to any specific therapeutic protocol because such details are well known to those of skill in the art, relying for support on MPEP2164.05(a). This is unpersuasive because Applicant presents evidence of only one such protocol, the use of Vitravene. As discussed above, antisense therapy is an unpredictable art, and a single example cannot enable the broad scope of the instant claims. Applicant's reliance on Dove is misplace because Dove was published after the time of filing, and because the fact that the compounds in Table 1 of Dove are in clinical trials is not evidence that they are pharmaceutically effective. See e.g. Dove at page 122, column 2, first full paragraph.

Finally, Applicant argues in the paragraph bridging pages 6 and 7 that there are many in vivo diagnostic methods based on antisense oligonucleotides. This is unpersuasive because it is unclear that any of the examples cited by applicant is an in vivo method. The abstract of Ishidou describe in situ hybridization in epidermal keratinocytes but is silent as to whether or not this was performed in vivo. Similarly it is unclear that the method of Eberhagen was performed in vivo. Clearly the assay could have been performed in vitro on isolated cells in situ. Gelmetti clearly teaches an in vitro technique as "samples were collected" and subsequently assayed. Similarly

Stowe teaches an in vitro assay, not an in vivo assay, as the detection step requires flow cytometry.

For all these reasons Applicants arguments are unpersuasive.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 9, and 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. In this case, use of the word "preferably" is considered to be equivalent to "such as". Note also,

for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 8, 9, and 24-26 recite the broad recitation "R3 is the chemical group", and the claim also recites R3 is preferably a -C(=O) group or an -NH-(=S) group" which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5, 8, 10-12, and 15-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Cook et al (WO94/01448, published 1/20/94).

Cook teaches oligonucleotides covalently linked to a variety of moieties, including an aryl conjugate which comprises an X-(C=Y)-R1 group and processes for preparing them. See abstract; and page 6, line 4, second structure. The oligonucleotide may be modified, see paragraph bridging pages 3 and 4. The aryl group is attached to the oligonucleotide via the chemical group C=O. See page 6, line 4, second structure. The aryl group may be attached to an amino reactive group, e.g. N6 of adenine. See page 4, last sentence. The compounds may be transferred across the cell membranes of bacterial cells, or human tumor cells. See e.g. list of

targets in the table bridging pages 18 and 19 particularly lines 5 and 11 on page 19. An excipient may be added to the composition. See pages 20 and 21. The compositions may be used in diagnostic probes. See pages 24 and 25. It is noted that, while these compositions of Cook are not considered to be enabled for pharmaceutical use, they are structurally indistinguishable to the compounds of claims 22-24, so these claims are properly rejected.

Thus Cook anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8, 11, 13, 14, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook et al (WO94/01448, published 1/20/94).

Cook teaches oligonucleotides covalently linked to a variety of moieties, including an aryl conjugate which comprises an X-(C=Y)-R1 group and processes for preparing them. See abstract; and page 6, line 4, second structure. The oligonucleotide may be modified, see paragraph bridging pages 3 and 4. The aryl group is attached to the oligonucleotide via the chemical group C=O. See page 6, line 4, second structure. The aryl group may be attached to an amino reactive group, e.g. N6 of adenine. See page 4, last sentence.

Cook is silent as to the pH at which the synthesis reaction must be carried out, and does not teach organization of the conjugate into a test kit.

With regard to claim 26, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize these conjugate into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

With regard to claims 13 and 14, it would have been obvious to one of ordinary skill in the art at the time of the invention to perform the reaction at pH 7 because the pH at which a reaction is performed is a result effective variable that is routinely optimized. Generally, differences in concentration of reactants, such as hydrogen ions, should not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that this concentration is critical. See MPEP 2144.05(b). "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955). In this case, the pH is not disclosed as critical. In any event, Cook teaches the formation of the same chemical structure, using the same required reactive group (an amine group), thus one would reasonably expect that the optimal pH of the reaction of Cook would be similar to that of the instant invention.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed. The elected species of a conjugate comprising F3 as an aryl group; oligonucleotides as a compound to be transported; and a carboxylic acid as a reactive function is free of the art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER